'competitive' environments. Although it is possible to imprint certain templates in polar environments, polar solvents (e.g. water) tend to interfere to an unacceptable level with the non-covalent interactions between template and functional monomer that are often relied upon in imprinting protocols. What is more common and easier to deal with, however, is the use of imprints effectively in buffer and/or polar environments. Finally, the imprinting of larger templates (e.g. proteins) is rather challenging at present due to their 'fragile' nature. New synthetic developments should lead to progress in this area also.

Conclusions

Molecularly imprinted polymers constitute a new class of sorbents which combine the robust character of cross-linked polymers with the attractive properties of natural receptors. In sample clean up and concentration for trace and ultra-trace analysis, they offer distinct advantages over both liquid–liquid extraction and solid-phase extraction using classical sorbents and immunosorbents. Besides analytical applications, imprinted polymers are being increasingly considered for preparative-scale SPE applications, even though their present low functional capacity sets a limit on their widespread utility. However, concomitant with improvements in their capacity, it will become increasingly appealing to use imprinted polymers to remove products and/or by-products from reaction vessels/streams, and to influence directly the course of chemical reactions by 'equilibrium shifting'. Finally, it is worth noting that the area of molecular imprinting as a whole is undergoing rapid expansion at present. What this implies for MISPE is that one can expect tailored, high-performance imprinted polymers to become increasingly attractive and more widely available as methodologies improve and breakthroughs are made.

See also: **II/Extraction:** Solid-Phase Extraction. **III/Immunoaffinity Extraction. Selectivity of Imprinted Polymers: Affinity Separation:**

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MOLECULAR RECOGNITION TECHNOLOGY IN INORGANIC EXTRACTION

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Selective ion recognition, binding and transport are important processes in living systems. From the active sites of metalloproteins, such as amine oxidase, to lower molecular weight ligands like valinomycin, the K^+-selective macrocyclic antibiotic, the underlying principles of such selective ion binding and utilization have for some time been the subject of intensive investigation and modelling by many researchers.

Table 1 Developments in macrocyclic host chemistry of major importance in ion recognition

von Baeyers (1872)	Origin of calixarenes in phenol-formaldehyde reactions
Meadow and Reid (1934)	Preparation of hexathia-18-crown-6 in low yield
Zinke and Ziegler: Niederl and Vogel (1940s)	Cyclic oligomeric structures assigned to products from phenol-formaldehyde reactions
Pedersen (1967)	Pioneering work on crown ethers, using picrate extraction
Rosen and Busch (1969)	Macrocyclic thioether ligands
Lehn, Sauvage and Diedrich (1969)	First macrobicyclic ligands, the cryptands
Gutsche (1978)	Introduced name calixarene and suggested potential as molecular receptors
Cram (1979)	Development of spherands, with more fixed pre-organized cavities for cation selectivity
Izatt and Christensen (1983)	Selective extraction of cesium ions by *p-tert*-butylcalixarenes in liquid membranes
Pedersen, Lehn and Cram (1987)	Nobel Prize in chemistry

Many new branches of chemistry have developed which aid the challenge, including supramolecular chemistry, the study of the formation and properties of larger molecular aggregates from the self-assembly of smaller complementary molecules through non-covalent intermolecular forces. Specifically, the creation of pre-organized cavities in synthetic host molecules for the selective reception of a neutral or ionic species is described as host–guest chemistry or molecular recognition, an approach gleaned from enzyme–substrate interactions. Macrocyclic ligands have received particular attention, as host molecules, since the pioneering work of Pedersen on the synthesis and metal extraction properties of crown ethers. This began a revolution in macrocyclic ligand and receptor design, acknowledged with the award of the Nobel Prize in chemistry in 1987 to three of the main contributing scientists, Pedersen, Lehn and Cram (**Table 1**), a revolution which continues today as new host molecules with unique selectivities of binding and mechanisms of release are produced.

Many macrocyclic ionophores are host molecules, which vary in the extent to which they are pre-organized for selective recognition of guest species and the fitting of guest to host in a complementary fashion. Some of the most important macrocyclic ligands are listed in **Table 2**. Cram recognized that the more highly organized the host was for binding and low solvation, prior to complexation, the greater would be complex stability. Greater cation selectivity resulted, using fixed pre-organized host cavities of controlled size, provided by such macrocycles as cryptands and spherands. The chemical structures of representative macrocyclic host molecules are given in **Figure 1**, alongside the ions which have been shown to reside selectively in the guest cavities. The concepts that cavity size and shape could be tailor-made and fine-tuned to suit the selected cation diameter, and that donor atom choice determines the cation selectivity, have caught the imagination of many chemists over the last 30 years. In particular, separation scientists have been quick to demonstrate selective metal extractions, such as the separation of trace amounts of silver from mercury using 14-thiacrown-4 and the extraction of mercury and lead by 18-crown-6. Important studies were carried out on monocyclic aza crowns and cryptands, which are macrobicyclic compounds, where the complexed cation is completely enclosed by ligands, containing O and N, in a central cavity. More recently, attention has been focused on calixarenes, which are a class of functionalized metacyclophanes possessing convergent phenolic groups arranged around the periphery of a central aromatic cavity. These macrocycles have been described by Shinkai as the third host molecule after cyclodextrins and crowns as the first two major impact host molecules. The unique ionophoric properties of functionalized calixarenes have been clearly demonstrated using nuclear magnetic resonance (NMR) spectroscopy and liquid–liquid extraction studies. Functionalization, at the upper and lower rim, can lead to an enormous number of derivatives, water- or organic-soluble, with varied ionophoric selectivities.

Table 2 Macrocyclic ligands

Molecular recognition ligands	*Examples of metals complexed*
Crown ethers	Na, K, Rb, Cs
Thiacrowns	Ag, Au, Pt, Hg
Azacrowns	Cu, Ni
Cryptands	Na, K, Rb, Cs
Spherands, hemispherands, cryptaspherands	Li, Na, K, Rb, Cs
Calixarenes	Cs, Fe, Cu
Calixarenes (functionalized)	Na, Cs, Ca, Pb, Ag, Fe, UO_2^{2+}
Calixcrowns	K, Cs

In this review, representative examples of these molecular recognition reagents and their roles in selective metal ion extraction are presented. The emphasis is on illustrating through examples the influences that contribute to selectivity of complexation and extraction, and on the new materials and

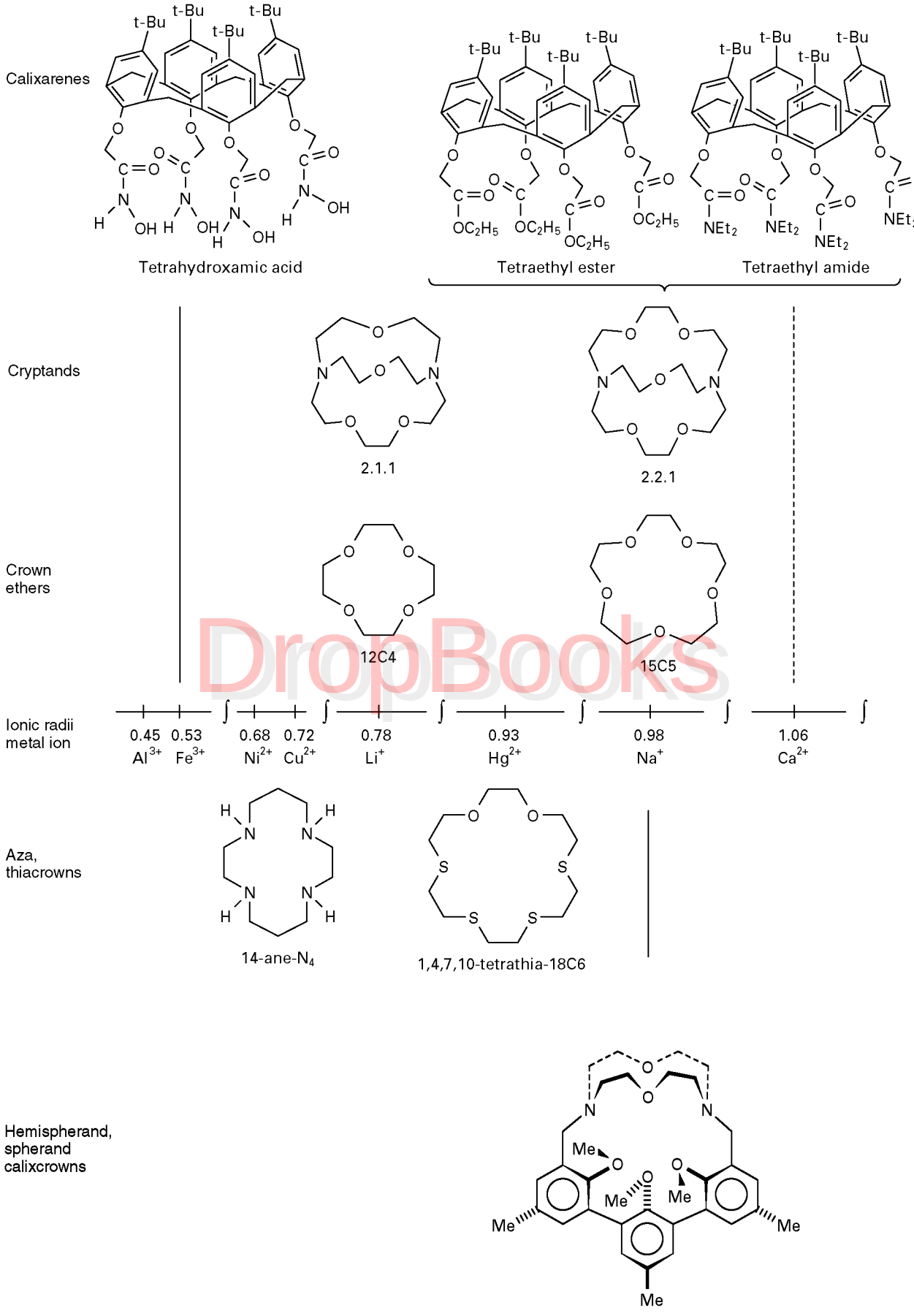

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Figure 1 Macrocyclic host molecules.

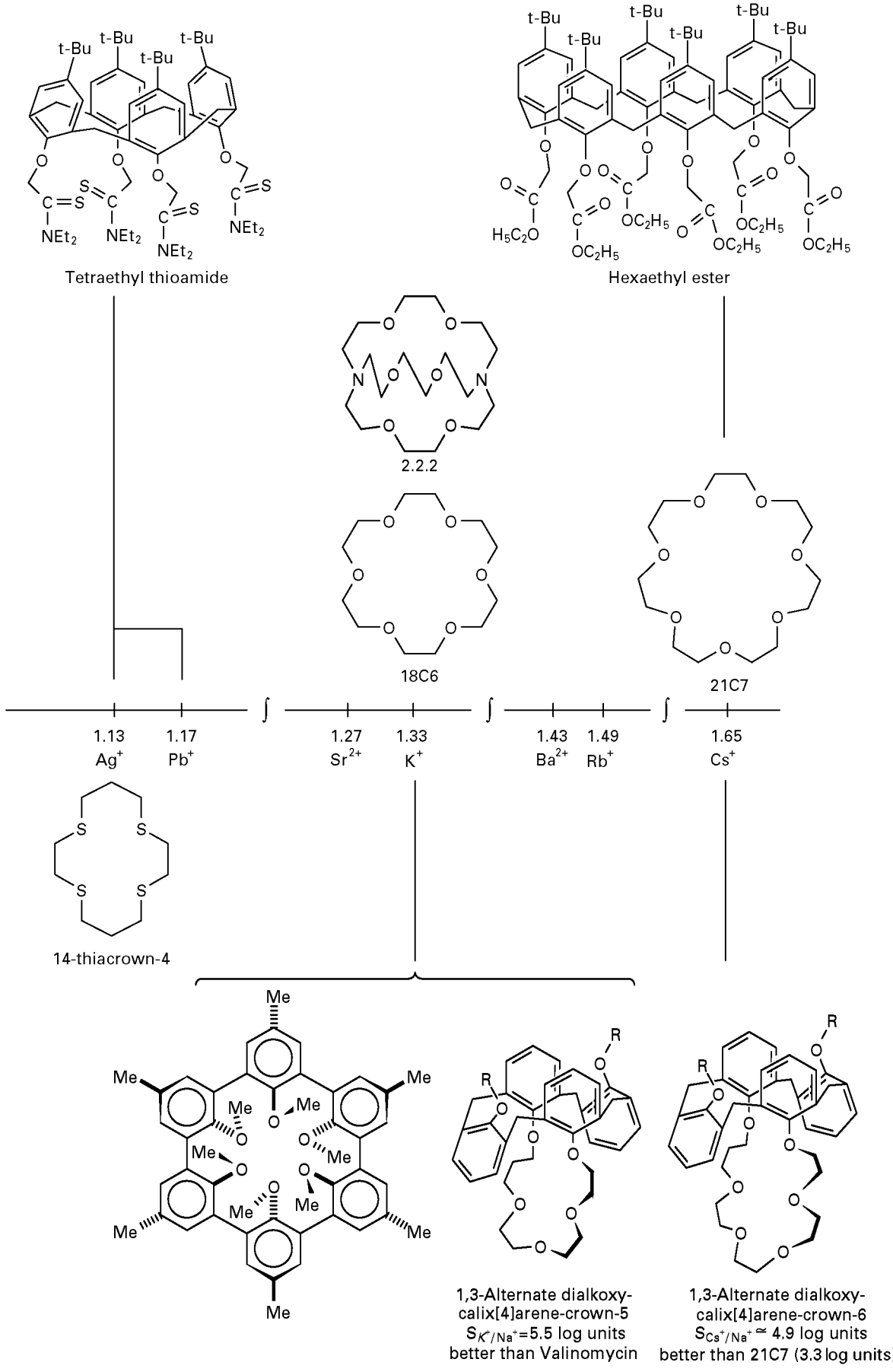

Figure 1 *Continued*

experimental approaches that have been adapted to demonstrate analytical and preparative-scale selective metal ion extraction using molecular recognition reagents.

Selectivity of Metal Ion Complexation

Determination of the selectivity of complexation is an important goal, since it gives further pointers to where the synthetic effort should focus, and it is a necessary step in assessing how far the synthetic design has progressed to meet the challenge presented by such natural ionophores as valinomycin.

The selectivity of molecular recognition ligands for metal ions is chiefly described in two ways, as the ratio of the measured stability constants for a pair of ions or from phase transfer and transport studies of selected cations from aqueous solution into organic solvents.

Ratio of Stability Constants

The stoichiometric stability constant K_s (sometimes symbol β) for the complexation of a metal ion, M, by a ligand, L, in solution at a constant ion strength, is defined as:

$$K_s = [ML]/[M][L]$$

in the simplest situation where a 1 : 1 complex is formed and where the square brackets refer to molarities of complex, free metal and free ligand in solution. This is commonly the situation when macrocyclic ligands are involved. Thus, when comparing the relative stabilities of complexation of two metal ions, M_1 and M_2, with the same macrocyclic ligand, the ratio of the stoichiometric stability constants is a useful measure of selectivity:

$$\text{Complexation selectivity } S_{M1/M2} = K_s(M_1L)/K_s(M_2L)$$

Extraction Selectivity

The picrate extraction method introduced by Pedersen places the MR reagent in an organic solvent, such as dichloromethane, in contact with an aqueous metal picrate solution. If complexation occurs the metal ion extraction is monitored by spectrophotometry, following the co-extraction of the highly coloured picrate counterion ($\lambda_{max} = 355$ nm, $\varepsilon = 14\,416\ \text{mol}^{-1}\,\text{L}\,\text{cm}^{-1}$) into the organic solvent. The percentage cation extraction is calculated as the ratio $100 \times (A_0 - A)/A_0$, where A_0 is the measured absorbance of an aqueous blank metal picrate solution without complexation reagent and A is the absorbance recorded in the aqueous layer after equilibration. The method is particularly suited to the extraction of alkali and alkaline earths, but has also been applied to the assessment of the percentage extraction of transition metal ions. Thus, a liquid–liquid extraction method is used to determine the percentages of extraction for a series of metal ions and frequently tabulated or plotted against ionic radii to illustrate the ion preference of the reagent.

Selectivity of Molecular Recognition Ligands

Among the factors that contribute to the selectivity of metal complexation by macrocyclic receptors is the complementarity in size of the host cavity to the cation diameter. In Figure 1 this is readily seen with the crown ethers, where selectivity moves from Li^+ to Cs^+ as the host varies from 12-crown-4 up to the larger 21-crown-7. This matching of cation diameter and cavity size is also evident in the illustrated cryptand and calixarene series, with, for example, in the latter, Cs^+ selectivity being displayed by the calix[6]arene hexaester derivative. The principle of pre-organization of the host cavity is evident in the ion complexation by macrocycles such as the cryptands and spherands, which display greater complexing power than the earlier crown ethers. The influence of the nature of the donor atom on the selectivity of complexation is also evident in the illustrated macrocyclic compounds. The hard and soft acid–base theory of Pearson is a useful guideline as to the behaviour, with oxygen donor atoms considered to be hard bases and nitrogen and sulfur soft bases. Alkali and alkaline earth metal cations, considered hard acids, are preferred by hard bases, while soft acids such as heavy metals are preferred by soft bases. Shifts towards the complexation of soft cations such as Ag^+, Pb^{2+} and Hg^{2+} are seen in the aza and thia crowns. It is also clearly seen in the versatile calixarene series, as for example among the tetrameric series where the change from ester to amide to thioamide moves the ion preference from Na^+, to Ca^{2+} and on to Pb^{2+} and Ag^+. Hancock has emphasized the role of chelate ring size within the macrocycle – an effect which influences the stability of complexation by such macrocycles as the azacrowns and the calixarene tetrahydroxamate, shown in Figure 1.

Of particular note is the influence of conformation on the stability and extraction of metal ions by molecular recognition compounds. This has been powerfully illustrated recently with calixcrowns, which are capable of cone, partial cone and 1,3-alternate conformations. Calixcrowns derived from calix[4]arenes, unsubstituted on the upper rim, can be fixed in the 1,3-alternate conformation, as shown in Figure 1.

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Table 3 Percentage extraction and log β values for alkali and alkaline earth metal ion complexation by selected functionalized calixarene derivatives

Host macrocycle		*Li*	*Na*	*K*	*Rb*	*Cs*	*Mg*	*Ca*	*Sr*	*Ba*
p-t-Bu-Calix[4]arene-tetraethylester	%E	15	**94.6**	49.1	23.6	48.9				
$S_{Na/K} = 400$	Log β	2.6	**5.0**	2.4	3.1	2.7				
p-t-Bu-Calix[4]arene-tetraethylamide	%E	63	**95.5**	74	24	12	9	**98**	86	74
$S_{Ca/Mg} > 7.8$ log units	Log β	3.9	**7.9**	5.8	3.8	2.4	1.2	$>$ **9**	>9	7.2
1,3-Dialkoxycalix[4]arene-crown-6	%E	2.5	2.6	13.8	41.7	**63.5**				
$S_{Cs/Na} > 4.9$ log units	Log β	<1.5	<1.5	4.3	6.0	**6.4**				
1,3-Dialkoxycalix[4]arene-crown-5		–	–	–	–	–				
$S_{K/Na} = 5.53$ log units	Log β	4.78	**4.30**	**9.83**	9.41	6.87				
Valinomycin		–	–	–	–	–				
	Log β	5.83	**6.09**	**9.35**	9.83	8.97				

Data compiled from Arnaud-Neu *et al.* (1989) and (1991), Dozol *et al.* (1997) and Casnati *et al.* (1996).
Bold figures, highest selectivity and extraction.

While the extraction and complexation profiles are strongly dependent on the size of the crown, the behaviour is dependent on the conformation, with the highest extraction and complexation levels found for the 1,3-alternate ligands. Two striking selectivities have been achieved, as shown in **Table 3**. Remarkable Cs^+/Na^+ selectivity ($S_{Cs/Na} > 4.9$ log units) was obtained for the 1,3-alternate calix[4]-crowns-6, making applications to the extraction of caesium from radioactive waste possible. The conformation has a direct bearing on the relative stabilities, with cation-π interactions possible for caesium but not for the smaller sodium in the rigid conformation. In addition, 1,3-alternate-calix[4]arenecrown-5 conformers have been shown in extraction experiments from water to chloroform to have better K^+/Na^+ selectivity ($S_{K/Na} = 5.53$ log units) than the naturally occurring ionophore, valinomycin.

Numerous functionalized calixarenes and, more recently, calixcrowns have been studied for their ability to extract metal ions and the stabilities of the metal–ligand complexes measured. In general, changes in the extraction profiles as the ion is varied mirror the changes in stability of the complexes. Four representative examples chosen to illustrate the influences of donor atoms and conformation on extraction and selectivity are provided in Table 3, alongside stability data reported for valinomycin.

Molecular Recognition Ligands in Inorganic Extraction

Solvent Extraction of Metal Cations

The Pedersen picrate extraction method is particularly suited to alkali and alkaline earths; using it McKervey *et al.* were able to show that *p–t*-butylcalix[4]arene esters and ketones were Na^+-selective over other alkali metal ions and that calixarene complexation of metal ions is determined by the cavity size and the type of functionalization.

In sample preparation prior to trace metal analysis, a well-established procedure is the extraction of transition and heavy metal ions such as Cu^{2+} and Pb^{2+} into methylisobutylketone using extraction reagents such as sodium diethyldithiocarbamate and dithizone. Extraction can be monitored by spectrophotometry, as many of the complexes are coloured, or by atomic absorption spectroscopy. While such liquid–liquid extraction methods using conventional extraction reagents achieve preconcentration and sample clean-up, today the challenge is for greater selectivity of extraction, even as far as the extraction of specific metal ions from complex matrices. This can be achieved by molecular recognition technology. As far back as 1983, Izatt *et al.* demonstrated selective extraction of Cs^+ through organic liquid membranes by macrocyclic *p-tert*-calix[n]arenes through the formation of neutral complexes following proton loss. Another illustrative example is the challenge of selective extraction of uranium from sea water, where lipophilic calix[6]arene carboxylates and phosphonates have been reported as uranophiles, capable of selective transport of UO_2^{2+} ions from water into organic media. In this manner, calixarenes functionalized with ionizable or chelating groups have been extensively studied over a range of pH for the extraction of transition and heavy metal ions from aqueous to organic solution. In particular, Shinkai has studied calix[5]- and calix[6]arenes with sulfonate, phosphonate, carboxylate and hydroxamate groups as uranophiles in extraction and transport experiments. The great strength of calixarenes as selective metal extraction reagents is that any chelating moiety can be attached to the macrocycle at the upper or lower rim for targeted metal ion extraction.

Extraction of Metal Ions using Molecular Recognition Solid Phases

The immobilization of extractants onto supports for solid-phase extraction has many advantages over liquid–liquid extraction, including minimization of the use of organic solvents and amenability to automation. Important approaches taken to immobilize extractants include dissolution in a support-held organic liquid and chemically bonded solid phases.

Supported liquid membrane enrichment technique The supported liquid membrane (SLM) enrichment technique involves using a solid membrane, such as porous polytetrafluoroethylene, which is impregnated with an organic solvent which acts as a stationary liquid positioned between two aqueous solutions (**Figure 2A**). When the membrane separator is configured to allow the use of flowing aqueous solutions, the technique can combine the selectivity and enrichment capabilities of liquid–liquid extraction with efficient matrix constituent removal for automated sample preparation. While the use of liquid membrane technology for extraction in industrial processes is well established, the use of SLM technology for analytical applications began in the mid 1980s for trace organic extraction. For trace metal extraction, recent examples have focused on the use of extractants such as 8-hydroxyquinoline and organophosphates. The use of a lipophilic diazo-18-crown-6 in an SLM for the separation of Cu^{2+} from natural water samples has been studied. SLM technology has in particular been used to complement liquid–liquid extraction studies in determining the selectivities of some of the more recently synthesized calixarene ligands. Further studies on the use of molecular recognition reagents in SLMs are likely to lead to further useful demonstrations of enhanced selectivities of extraction using molecular recognition ligands.

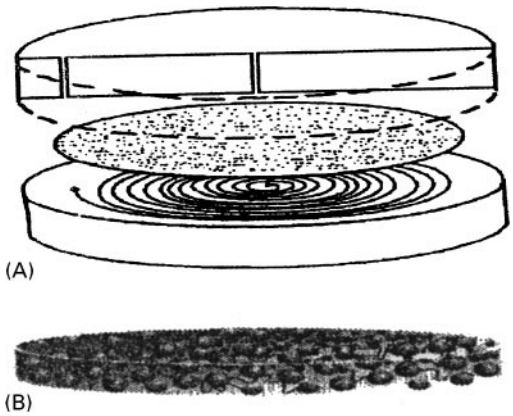

Figure 2 (A) Supported liquid membrane and (B) particle-loaded membrane.

Solid-phase extraction technology This approach to the extraction of metal ions involves the partitioning or complexation of the metal species from the aqueous phase onto a solid phase, usually a polymer or silica. From literature reviews of solid-phase extraction, it is clear that chemically bonded phases derived from liquid chromatography are generally used for organic solute extraction. For metal ions, ion exchange and chelating phases have been widely used and have clear advantages over liquid sorbent-based approaches. How molecular recognition has impacted and can further impact on this approach to extraction will be seen from the next illustrative examples.

Silica-bond thiacrown macrocycles Considerable work has been done on the chemical attachment of crown ethers to silica and polymeric supports for chromatographic separation of ions and chiral solutes. Separations of alkali and alkaline earths using water-based eluents have been demonstrated and ion-modulated separations carried out. For inorganic extraction, by far the greatest impact has been made with silica-bonded thiacrown phases. Highly selective silica-bonded, sulfur-containing crown phases are commercially marketed in packed beds or columns as SuperLig™ and AnaLig™ (for industrial and analytical separations, respectively) by IBC Advanced Technologies (Provo, UT, USA). These molecular recognition materials have resulted from the research work of Izatt *et al.* at Brigham Young University, and have been applied to the extraction of targeted metals in complex matrices, such as the large scale removal of Pd^{2+} from $AgNO_3$ streams, the removal of Cs^+, Sr^+ and Pb^{2+} from nuclear waste streams, and for analytical extractions, to the concentration and analysis of low level Hg^{2+}. The selectivity of silica-bound 1,4,7,10-tetrathia-18-crown-6 for Hg^{2+} over Ag^+ is reported as 10^6; in comparison, the selectivity of a typical ion exchange resin for Ag^+ over Hg^{2+} is 1.06.

Particle-loaded membranes The incorporation of solid-phase extraction particles into a web of microfibrils to form an extraction membrane with fast mass transfer kinetics has been described (Figure 2B). Highly selective and efficient removal of metal ions from solution is possible; for example, rapid sample processing and determination of radioactive strontium, counted from the surface of the membrane disc, can be achieved using Empore™ Strontium Rad Disks, containing AnaLig™ molecular recognition technology.

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Silica-bound molecular baskets for extraction and chromatography Molecular baskets, as calixarenes have been described, can be immobilized onto solid supports to yield new molecular recognition materials for extraction and chromatography. The obvious supports are polymer and silica phases. The nature of the surface silica-bound species in chemically bonded molecular baskets on silica has been elucidated using solid-state NMR spectroscopy. When packed as a chromatography column, a silica-bonded calix[4]arene tetraamide phase displayed significant retention of Ca^{2+} over Mg^{2+}, a result in keeping with the reported high complexation selectivity of the calixarene for Ca^{2+} over Mg^{2+} ions. For transition metal ion extraction, a macrocycle that combines the sequestering ability of siderophores with the ionophoric properties of calixarenes is another interesting example of these new phases. Calix[4]arene tetrahydroxamic acid can be chemically bonded to silica particles or partitioned onto a solid support. Metal uptake profiles as a function of pH have been determined using solid-phase extraction cartridges filled with these new molecular recognition phases and the phases have been characterized by diffuse reflectance infrared Fourier transform (DRIFT) and solid-state NMR spectroscopy. The molecular recognition phase is capable of selective removal of Pb^{2+} and Fe^{3+} from acidic aqueous solution with Ni^{2+}, Zn^{2+}, Co^{2+}, Mn^{2+} and Cd^{2+}. The complexation of Pb^{2+} takes place at a more acidic pH than is achievable with linear hydroxamic acids, as a result of host–guest complexation in the basket cavity. The structure of the silica-bonded molecular basket is schematically given in **Figure 3**, with coupling through two of the three available ethoxy groups on the derivatized upper rim. The sites for complexation of metal ions are shown on the lower rim. (It is acknowledged that there is a redundant hydroxamate group in the tetrahydroxamate when metal ions are complexed in an octahedral fashion.)

Supercritical Fluid Molecular Recognition Technology for the Extraction of Metal Ions

Instead of carrying out liquid–liquid extractions or solid-phase extractions for the pretreatment and preconcentration of metal ions from solid and liquid matrices, it is possible to send in a selective courier molecule to permeate through the sample, grab on to the targeted metal and deposit it in concentrated form into a collection vessel for further analysis. Such a technology utilizes the solvating power of supercritical CO_2 and the metal–ion complexing power and selectivity of organic ligands, and is currently the focus of considerable research attention. Several studies have been reported on the supercritical fluid extraction (SFE) of metal ions via the formation of

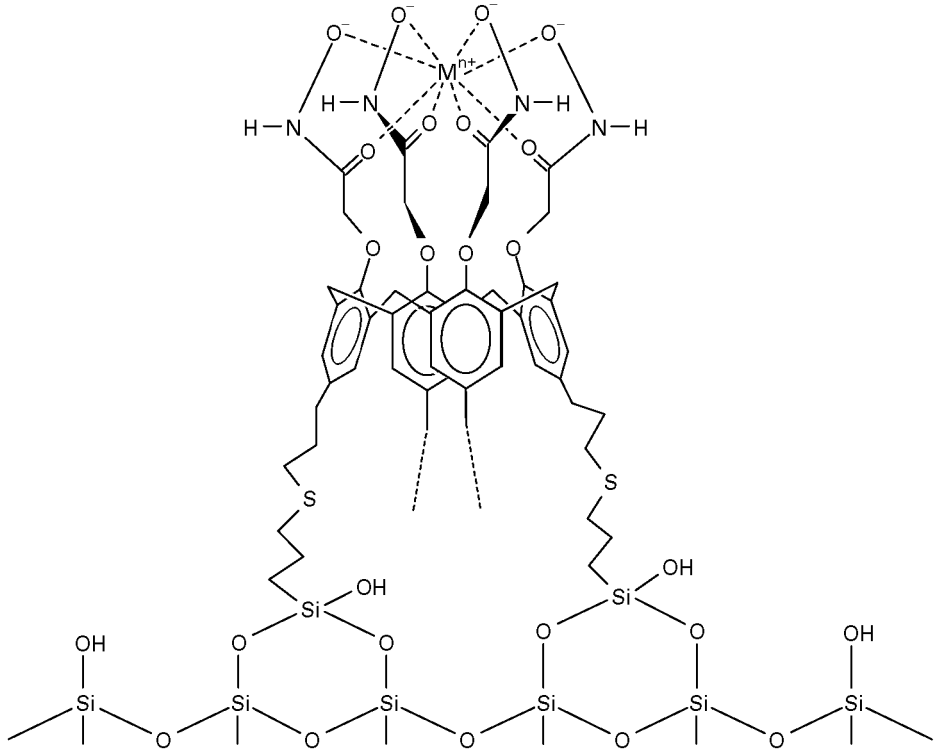

Figure 3 Proposed structure of silica-bonded calix[4]arene tetrahydroxamate phase.

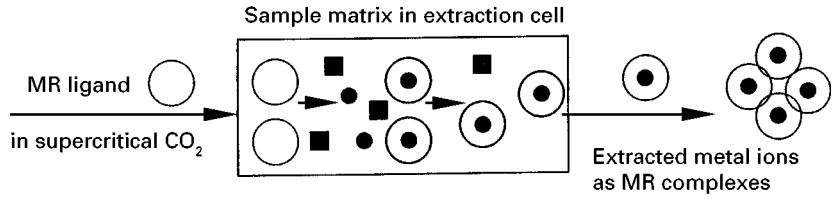

Figure 4 Schematic diagram of selective SFE of targeted metal ions using macrocyclic extractants. Filled circles, targeted metal ions; filled squares, diverse metal ions.

neutral metal–ligand complexes resulting in useful solubilities in supercritical CO_2. These solubilities can be improved by several orders of magnitude by substituting fluorine for hydrogen in the chelating ligand. For example, β-diketones and dithiocarbamates have been fluorinated and successfully used as metal extraction reagents in SFE.

More advanced complexation in SFE is achievable using molecular recognition ligands, where enhanced selectivity of extraction is achievable by careful choice of donor atoms and host cavity size in a macrocyclic reagent, as illustrated in **Figure 4**.

Recently, such selective extractions using macrocyclic reagents in SFE has been demonstrated. The selective extraction of mercury from sand, and cellulose filter paper using ionizable dibenzobistriazolo crown ether in methanol-modified supercritical CO_2 has been reported. The synthesis and use of fluorinated molecular baskets for metal extraction in unmodified supercritical CO_2 has been described. Fluorinated calixarenes are the templates on which carefully selected chelating groups can be incorporated around the cavity to yield selective extractants for targeted metals. The ability of one such molecular basket, a fluorinated calix[4]arene tetrahydroxamate, selectivity to extract Fe^{3+} from metal mixtures on cellulose paper has been monitored using atomic absorption analysis (**Figure 5**). Further examples of where targeted metal ions in a matrix, present as unwanted contaminants or as valuable metals to be recovered, are selectively complexed and removed by such macrocyclic extractants dissolved in supercritical CO_2 are likely in the future.

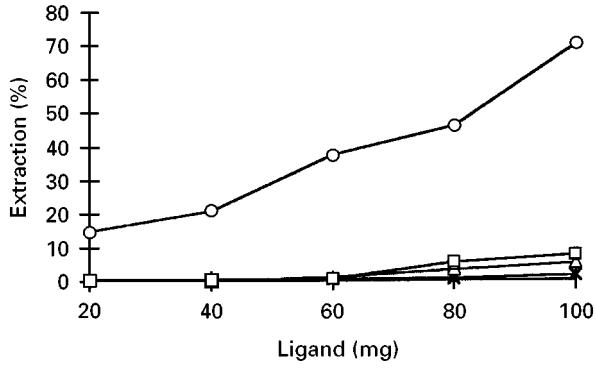

Figure 5 Percentage extraction of metal ions, as determined by atomic absorption analysis, versus mass of fluorinated calixarene tetrahydroxamate reagent used in the SFE of p.p.m. levels of Fe^{3+} (circles), Cu^{2+} (squares), Ni^{2+} (triangles) and Mn^{2+} (crosses) from spiked cellulose paper. 40 μL of water, 60°C, 350 atm, 30 min static and 15 min dynamic.

Future Developments

Molecular recognition ligands for metal extraction are likely in the future to be cage-like and pre-organized to provide the preferred symmetry of the targeted metal ion. Higher selectivities of extraction for cations and anions can be expected, by reagents which subsequently release the guest under an applied stimulus. Molecular recognition speciation, allowing preferential extraction of individual oxidation and chemical species, will receive more attention. In chemical analysis, the incorporation of molecular recognition into miniaturized extraction devices or layers followed by detection will be further examples of the powerful role of designed molecular recognition reagents in inorganic extraction.

See also: **II / Affinity Separation:** Immobilised Metal Ion Chromatography: **Extraction:** Analytical Inorganic Extractions; Solid-Phase Extraction; Supercritical Fluid Extraction. **III / Ion Analysis:** Liquid Chromatography; **Metal Complexes:** Ion Chromatography; **Solid-Phase Extraction With Disks.**

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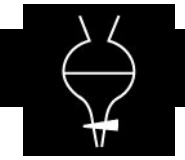
MULTIRESIDUE METHODS: EXTRACTION



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Introduction

'Killing two birds with one stone' is a common expression that captures the essence of multiresidue methods of analysis. Multiresidue methods are almost always more efficient than separate single analyte methods for multiple analytes. However, a possible drawback of multiresidue methods that cover a wide polarity range or diversity of analytes is a potential loss of selectivity for individual analytes. The use of high efficiency analytical separation techniques and/or very selective detectors can compensate for a lack of selectivity in preceding steps, but as a general rule, a greater degree of selectivity leads to higher quality results. Multiresidue methods often involve a balancing act between the analytical scope of the method and the quality of the results for all analytes. It is sometimes difficult 'to have your cake and eat it, too'.

Residues

In general, residues consist of synthetically derived chemicals that are not intended to occur in the sample, but may be present at trace concentrations as a by-product of a preliminary process related to the sample, or as a separate process altogether. Residues may be inorganic or organic, but inorganic compounds are generally analysed separately from organics. Multielemental analysis measures the natural occurrence of elements as well as any residues that may occur in the sample. Microorganisms and dirt may also be considered residues according to some definitions, but their analysis requires different techniques from organic compounds and they will not be considered further in this discussion. In the case of organic chemicals, many natural components are capable of being analysed in the same approach as the residue method, but these compounds are usually termed interferences, and great effort is often spent trying selectively to remove or avoid them (however, other chemists may be very interested in these matrix interferants).

The most common type of multiresidue application is the analysis of organic chemical contaminants in food and environmental samples. There are instances